APPENDIX

List of drugs approved by the Food and Drug Administration for the indication of Acute Exacerbations of Chronic Bronchitis

Bactrim Pediatric Suspension (Roche Laboratories)
Bactrim Tablets (Roche Laboratories)
Bactrim DS Tablets (Roche Laboratories)
Biaxin Filmtab Tablets (Abbott)
Biaxin Granules (Abbott)
Ceclor CD Tablets (Dura)
Cedax Capsules (Schering)
Cedax Oral Suspension (Schering)
Ceftin Tablets (Glaxo Wellcome)
Cefzil for Oral Suspension (Bristol-Myers Squibb)
Cefzil Tablets (Bristol-Myers Squibb)
Cipro Oral Suspension (Bayer)
Cipro Tablets (Bayer)
Floxin I.V. (Ortho-McNeil Pharmaceutical)
Floxin Tablets (Ortho-McNeil Pharmaceutical)
Levaquin Injection (Ortho-McNeil Pharmaceutical)
Levaquin Tablets (Ortho-McNeil Pharmaceutical)
Lorabid Suspension and Pulvules (Lilly)
Maxaquin Tablets (Unimed)
Omnicef Capsules (Parke-Davis)
Omnicef for Oral Suspension (Parke-Davis)
Primaxin I.M. (Merck)
Raxar Tablets (Glaxo Wellcome)
Septra Suspension (Monarch)
Septra Grape Suspension (Monarch)
Septra Tablets (Monarch)
Septra DS Tablets (Monarch)
Spectrobid Tablets (Pfizer)
Suprax for Oral Suspension (Lederle Labs)
Suprax Tablets (Lederle Labs)
Vantin Tablets and Oral Suspension (Pharmacia & Upjohn)
Zagam Tablets (Rhone-Poulenc Rorer)

/S/ 11/1/99

Ziad Akl, M.D.
Reviewing Medical Officer
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Concurrences:

/S/

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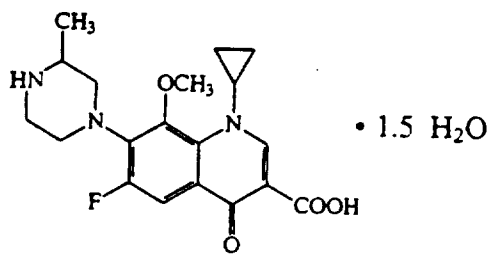
cc:
Original NDA 21-061
HFD-590/Div. Dir/Goldberger
HFD-590/Dep. Div. Dir/Albrecht
HFD-590/TL/Cavaillé-Coll
HFD-590/MO/Korvick
HFD-590/MO/Akl
HFD-590/Chem/Smith
HFD-520/Micro/Altaie
HFD-880/BioPharm/Uhl
HFD-520/Pharmtox/Ellis
HFD-725/Biometrics/Silliman
HFD-590/RPM/Atkins

8.3 Medical Officer Review of NDA 21-601: Gatifloxacin (Tequin ™) for the treatment of Acute Sinusitis

Date Submitted: 28 December 1998
Date Received : 29 December 1998
Date Assigned: 29 December 1998
Date Completed: 15 October 1999

Applicant: Bristol-Myers Squibb Company
5 Research Parkway
Wallingford, Connecticut 06492
203-677-6883
Contact person: Douglas Kriesel, Ph.D.

Drug: Proprietary name - Tequin ™
Generic name - Gatifloxacin
Chemical name - (±)-1-Cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolone carboxylic acid sesquihydrate
Molecular formula - $C_{19}H_{22}FN_3O_4 \cdot 1.5\ H_2O$
Molecular weight - 402.42 (sesquihydrate)
Molecular structure -



• 1.5 H_2O

Drug Class: 8-methoxyfluoroquinolone antibacterial

Formulation: (capsule, suspension, lyophilized powder, etc.)

Route of administration: Oral; 200 mg and 400 mg tablets (21-061)

Related NDA: 21-061, 21-062 [redacted]

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Medical Officer Executive Summary

The sponsor submitted three clinical studies in support of the acute bacterial sinusitis indication for gatifloxacin:

Protocol	Study Type	Dose/Frequency/Duration	Number of Patients
AI420-008	Multicenter, randomized, double-blind, controlled trial	Gatifloxacin 400 mg qd for 10 days Clarithromycin 500 mg bid for 14 days	Gatifloxacin 211 enrolled, 146 evaluable Clarithromycin 214 enrolled, 157 evaluable
AI420-007	Multicenter, open-label, uncontrolled trial	Gatifloxacin 400 mg qd for 10 days	Gatifloxacin 445 enrolled, 339 evaluable
AI420-066*	Multicenter, randomized, double-blind, controlled Trial	Gatifloxacin 400 mg qd for 10 days Trovafloxacin 200 mg qd for 10 days	Gatifloxacin 124 enrolled, 113 evaluable Trovafloxacin 131 enrolled, 115 evaluable

*Study No. AI420-066 was submitted to the NDA as a major amendment on June 11, 1999.

The three studies were generally similar in design. Study AI420-008 and AI420-066 were conducted at U.S. study sites, but Study AI420-007 also enrolled patients from Mexico, Argentina, Australia, and South Africa. Protocol inclusion criteria required baseline radiographic evidence of infection and the presence of two "cardinal" symptoms associated with acute maxillary sinusitis: purulent nasal discharge and facial pain/tenderness. A further requirement for symptom duration less than 28 days lessened the likelihood of enrolling patients with chronic sinusitis. In all studies, gatifloxacin was administered as a single 400 mg oral daily dose for 10 days. Patient assessments as outlined in the protocols were performed at baseline (within 48 hours before dosing), during the study (Day 3 to 5 of therapy), near the end of therapy (Day +1 to +5), post-therapy (Day +7 to +14) and at a final follow-up visit (Day +21 to +28). In the final efficacy analyses, the test of cure time window for studies AI420-008 and AI420-007 was +19 to +30 days following completion of therapy. In contrast, a Day +7 to +14 test of cure time window was used for Study AI420-066 (which also included a final follow-up assessment at Day +21 to Day +28 as a secondary efficacy endpoint). All microbiological efficacy data in support of this indication were obtained from antral taps performed in the uncontrolled, open-label AI420-007 study.

The following two tables summarize the clinical efficacy data for the clinically evaluable and all-treated patients populations according to the sponsor and the FDA medical officer analyses, respectively:

Clinical Efficacy of Gatifloxacin and Comparators in Acute Sinusitis (per Sponsor)

Study	Drug	Clinically Evaluable Patients		All-Treated Patients	
		Efficacy Rate	95% C.I.*	Efficacy Rate	95% C.I.*
AI420-008	Gatifloxacin	72% (105/146)	(-15.2, 6.7)	62% (131/210)	(-10, 9.6)
	Clarithromycin	76% (119/157)		63% (132/211)	
AI420-007	Gatifloxacin	79% (276/339)	(76.9%,85.4%)	78% (329/424)**	(73.3%,81.5%)
AI420-066	Gatifloxacin	88% (99/113)	(-9.6, 12.2)	80% (99/123)	(-7.2, 16.1)
	Trovafloxacin	87% (100/116)		76% (100/131)	

*95% confidence interval (C.I.) refers to point estimate for gatifloxacin efficacy rate in Study AI420-007 and refers to the difference in efficacy rates for the remaining studies

**Eligible patient population

Clinical Efficacy of Gatifloxacin and Comparators in Acute Sinusitis (per Medical Officer)

Study	Drug	Clinically Evaluable Patients		All-Treated Patients	
		Efficacy Rate	95% C.I.*	Efficacy Rate	95% C.I.*
AI420-008	Gatifloxacin	61% (89/146)	(-16.5, 6.6)	54% (113/210)	(-9.0, 11.0)
	Clarithromycin	66%(103/157)		53% (112/211)	
AI420-007	Gatifloxacin	79% (276/339)	(76.9%,85.4%)	78% (329/424)**	(73.3%,81.5%)
AI420-066	Gatifloxacin	88%(94/107)	(-7.0, 15.8)	80% (99/123)	(-5.8, 17.7)
	Trovafloxacin	84%(94/112)		75% (98/131)	

*95% confidence interval (C.I.) refers to point estimate for gatifloxacin efficacy rate in Study AI420-007 and refers to the difference in efficacy rates for the remaining studies

**Eligible patient population

In general, the gatifloxacin efficacy rates at the test of cure visit were above 70% in clinically evaluable patients. The response rate of 61% in the FDA analysis for the clinically evaluable gatifloxacin patient population in Study AI420-008 was based on a conservative analysis requiring complete resolution of both nasal purulence and facial pain/tenderness (i.e., the two "cardinal" signs/symptoms of acute sinusitis). Using the original protocol-specified equivalence delta of 0.15 (based on projected response rates of 80-90%), this study was only marginally supportive of gatifloxacin's equivalence to the approved comparator agent, clarithromycin by either the sponsor's or FDA's analysis. However, the sponsor maintains that an equivalence delta of 0.20

should be applied due to the lower than anticipated response rates. Using this new definition, equivalence is demonstrated.

The second, supportive, comparator-controlled clinical trial (AI420-066) was submitted as a major amendment to the NDA on June 11, 1999. As shown in the table above, gatifloxacin was clearly shown to meet the protocol-specified criteria for equivalence to the approved comparator, trovafloxacin. Finally, the open-label, uncontrolled Study AI420-007 provided a similar clinical efficacy rate (79%) for gatifloxacin to the two randomized, comparative trials. Taken together, these three studies provide convincing evidence that gatifloxacin is a clinically effective antimicrobial agent for use in acute sinusitis.

Study AI420-007 was designed to provide evidence of bacteriological efficacy against the three major pathogens in acute sinusitis: *Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis.* A total of 445 patients were enrolled in the study yielding 119 microbiologically evaluable patients. The overall bacteriological eradication rate for the microbiologically evaluable patients was 82%. Eradication rates for *Streptococcus pneumoniae* and *Haemophilus influenzae* were 89% (39/44) and 77% (17/22), respectively. While gatifloxacin appeared to demonstrate activity against six of seven penicillin-resistant *S. pneumoniae* infections, the small number of isolates in this study would be insufficient to support labeling for resistant organisms. Only six microbiologically evaluable patients with *Moraxella catarrhalis* isolates were enrolled in the study with an overall eradication rate of 67% (4/6). Of the three isolates from U.S. study sites, only one was eradicated. According to the DAIDP Points to Consider Document, the NDA should demonstrate activity against approximately 25 isolates of *S. pneumoniae* and *H. influenzae,* and 15 isolates of *M. catarrhalis* to support an acute sinusitis indication. Thus, the microbiological efficacy data from this study would support labeling for *Streptococcus pneumoniae* and *Haemophilus influenzae*, but not *Moraxella catarrhalis.*

The safety profile within the NDA is based on a total of 775 patients exposed to gatifloxacin. The most commonly reported drug-related adverse clinical events were mild in severity and related to the gastrointestinal tract (nausea, diarrhea, vomiting, dyspepsia, and abdominal pain). Dizziness was uncommonly reported in studies AI420-008 and AI420-007 ($\leq$ 3% of patients) but was reported in 26% of subjects in study AI420-077. This discrepancy may be due to the use of trovafloxacin as the comparator agent in the latter study. The very high incidence of dizziness in trovafloxacin-treated patients (53%) in this study may have increased the attention of the investigators and/or the patients to this symptom.

Of note, a total of 5 patients treated with gatifloxacin had to withdraw from the studies due to possible Type I hypersensitivity reactions. In three patients, the reaction was manifested by generalized hives/welts and pruritis. Two other patients experienced transient tongue edema and throat tightness, respectively. All five patients were managed successfully with conservative therapy (e.g., antihistamines), and none

required hospitalization. While not clearly allergy-mediated drug reactions, these two cases raise concern regarding the potential for anaphylactic reactions in patients receiving gatifloxacin therapy. While the proposed label clearly states that gatifloxacin may be associated with hypersensitivity reactions and should be discontinued at the first signs of such reactions, FDA review of post-marketing adverse events should include a heightened awareness of this concern.

The following other adverse clinical events associated with the fluoroquinolone class were not reported in the gatifloxacin trials for acute sinusitis: hepatotoxicity, seizures, psychosis, tendonopathy, phototoxic skin rashes, cardiac abnormalities (although electrocardiograms were not routinely obtained during the studies to assess effects on QT interval).

The effects on clinical laboratory values in patients with normal baseline values were generally uncommon and mild in severity. The most common were hyponatremia and elevation or decrease in serum bicarbonate. Effects of gatifloxacin on liver function tests were typically mild and either of similar or lesser severity than the approved comparator agent. No patients were discontinued from the study due to the development of abnormal laboratories associated with gatifloxacin therapy. Of note, incomplete serum glucose data was submitted with the original NDA database. This data was submitted as an amendment and will be reviewed across all indications as part of the integrated summary of safety (per Dr. Korvick).

In conclusion, the medical officer recommends approval of gatifloxacin for the treatment of acute sinusitis due to *Streptococcus pneumoniae* and *Haemophilus influenzae*. Insufficient data were presented in the sinusitis section of the NDA to support labeling of acute sinus infections due to *Moraxella catarrhalis* or penicillin-resistant strains of *Streptococcus pneumoniae*. CEFTIN® was previously granted a similar indication for "**Acute Bacterial Maxillary Sinusitis** caused by *Streptococcus pneumoniae* or *Haemophilus influenzae* (non-beta-lactamase-producing strains only)." Following CIPRO® and LEVAQUIN®, gatifloxacin would represent the third fluoroquinolone antimicrobial agent approved by FDA for this indication (see APPENDIX I).

8.3.1 Study No. AI420-008: "A Randomized Double-Blind Multicenter Phase III Comparison of Gatifloxacin to Clarithromycin in the Treatment of Patients with Acute Maxillary Sinusitis"

8.3.1.1 Objectives:

- To establish the clinical efficacy of gatifloxacin at a dose of 400 mg QD for 10 days in the treatment of acute and uncomplicated maxillary sinusitis based on the resolution of signs and symptoms of sinusitis;
- To evaluate the safety profile of gatifloxacin, 400 mg PO QD, in this subject population; and
- To compare the safety and efficacy of gatifloxacin, 400 mg PO QD for 10 days, to a standard regimen of clarithromycin, 500 mg PO BID daily for 14 days.

MO Comment: The objectives of the study are clearly stated. Clarithromycin has an approved indication for acute bacterial sinusitis due to *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae* at the dosage, frequency and duration used in this study and therefore represents an appropriate comparator agent.

8.3.1.2 Protocol overview

This study was a Phase III, two arm, randomized (1:1), double-blinded. multicenter clinical trial designed to assess the safety and efficacy of gatifloxacin (400 mg PO QD for 10 days) compared to an FDA-approved comparator agent, clarithromycin (500 mg PO BID for 14 days), for the treatment of adults with acute, uncomplicated maxillary sinusitis.

The study was conducted at 23 sites in the United States and at 6 sites in Canada from September 18, 1997 through April 9, 1998.

8.3.1.10 Inclusion Criteria:

Patients had to satisfy all of the following criteria to be eligible for enrollment:

- Have the following clinical signs and symptoms consistent with an acute maxillary sinus infection (duration of signs and symptoms of sinusitis for $\leq$ 28 days):

  Facial pain/tenderness over one or both maxillary areas, and either

  a) purulent discharge from the maxillary sinus orifice, *or*
  b) purulent discharge from the nose, *or*
  c) purulent discharge present in the back of the throat.

- Radiological documentation of sinusitis (x-ray or CT scan) must be obtained to confirm the clinical diagnosis of sinusitis. The radiographs are considered supportive of the diagnosis if at least one of the following is evident in one or both maxillary sinuses:

  a) opacification
  b) an air/fluid level, or
  c) mucosal thickening of $\geq$ 5 mm

- Eighteen years of age or older;
- Written informed consent of the subject or a legally authorized representative;
- All women of childbearing potential (WOCBP) must have a documented negative serum or urine pregnancy test (minimum sensitivity 25 IU/L of beta-HCG) within 48 hours prior to the start of study medication; and
- All women of childbearing potential must agree to use an effective method of contraception from initiation of study medication until completion of the post-treatment procedures.

8.3.1.4 Exclusion Criteria:

Subjects meeting any of the following criteria at the time of enrollment were not eligible for the study:

- Chronic presentation of the current episode of sinusitis, defined as duration of symptoms longer than 28 days;
- Complicated sinusitis (e.g. Pott's puffy tumor, malignancy involving the sinus, osteomyelitis, contiguous bone infection, or requiring reconstructive surgery);
- Anatomic abnormality involving the maxillary sinus ostium which would impair drainage of the sinus and which might affect the response to therapy (e.g., post-traumatic or post-surgical defect);
- Recent sinus surgery (i.e., within 3 months prior to enrollment);
- Nosocomial sinusitis secondary to head trauma or nasotracheal intubation;
- Receipt of systemic antibiotic therapy within the 14-day period prior to enrollment, or likelihood of receiving other systemic antibiotics during enrollment in the study;
- Subjects who, in the opinion of the Investigator, would require long-term (greater than 14 days) antibacterial therapy;
- Subjects with cystic fibrosis;
- Subjects who are known to be HIV positive;
- Concurrent terfenadine treatment;

- Current clinically significant hepatic disease (i.e., ALT and/or AST and/or total bilirubin ≥ 3 times the upper limit of normal);
- Known renal insufficiency (e.g. serum creatinine ≥ 1.5 mg/dL or requiring dialysis);
- Previous treatment in any gatifloxacin clinical trial;
- History of a serious hypersensitivity reaction to any fluoroquinolone compound;
- Malabsorption syndromes or other gastrointestinal disturbances affecting drug absorption; or
- Pregnancy and/or breast feeding.

MO Comment: The inclusion/exclusion criteria are generally acceptable for defining an adult patient population with uncomplicated, acute maxillary sinusitis. However, the reviewer notes the following:

- **While the criteria specify that signs and symptoms at presentation should not exceed 28 days (to avoid enrollment of patients with subacute or chronic sinusitis), no minimum duration of signs and symptoms is required. The DAIDP Evaluability Criteria Guidance document recommends that symptoms be present for at least seven days to minimize the enrollment of patients with viral rhinosinusitis in clinical trials for acute bacterial sinusitis.**
- **Purulence discharge at the maxillary sinus orifice is listed as an inclusion criterion. However, the maxillary sinus orifice is anatomically concealed from view by a thin, bony projection from the lateral wall of the nasal cavity (uncinate process). Thus, the orifice is not normally visible on examination unless this structure has been surgically removed. However, purulence can often be visualized from the *middle meatal* region in acute bacterial sinusitis.**
- **With respect to radiological diagnosis, both CT scan and plain films are acceptable modalities for documenting acute sinusitis, although most published studies and guidelines use a cutoff of 6 mm of mucosal thickening (rather than the 5 mm cutoff used in this study) as supportive of a diagnosis of acute sinusitis.**

8.3.1.5 Randomization

Patients were randomized using a centralized telephone system that used a dynamic balancing algorithm to adjust randomization probabilities in order "to minimize any imbalance in treatment arms within each site and for the overall study.

MO Comment: Please refer to the Statistical Review for a thorough discussion of this unconventional randomization strategy.

8.3.1.6 Blinding

Study medication was administered in a double blind, "double dummy" fashion in order to mask differences in dose regimen and duration between treatment arms. All patients received blister cards containing matching active and placebo tablets for BID treatment over the 14 day study period.

Investigators could break the blind, following approval of the sponsor, only in medical emergencies when it was felt that the blind compromised a patient's safety. Unblinding of all patients in the study did not occur until all data were reviewed, entered, and the database was locked.

MO Comment: The study was adequately blinded.

8.3.1.10 Study Procedures/ Observations

The following table summarizes the study procedures and patient assessments during the trial (from the NDA, Volume 13, pg. 32):

Flow Chart: Schedule of Patient Assessments
Protocol AI420-008

Procedure	Pre-treatment (within 48 hrs prior to dosing)	During Treatment (Day 3 to Day 5)	End of Treatment (Day +1 to Day +3)	Post-treatment[a] (Day + 7 to Day +14)	Final Follow-up (Day + 21 to Day +28)
Informed Consent	X	-	-	-	-
Inclusion/Exclusion	X	-	-	-	-
Sinus Radiograph	X	-	-	-	X
Medical History	X	-	-	-	-
Physical Exam	X	-	X	-	X
Nasal Exam	X	-	X	-	X
Vital Signs	X	X	X	-	X
Clinical Signs and Symptoms	X	X	X	X[b]	X
Laboratory Tests	X	X	X	-	X[c]
Adverse Event Reporting	-	X	X	X	X
Assess Medication Use	-	X	X	-	-
Pregnancy Test	X	-	X	-	-

[a] Telephone contact

[b] If not clinically improved, the patient should be scheduled for an office visit for completion of the procedures outlined for the post-treatment visit (Section 5.8.5).

[c] If clinically indicated (i.e., all abnormal during/post-treatment laboratory test results should be repeated until they return to pre-treatment levels).

Note: Laboratory tests included the following: WBC with differential, hemoglobin, hematocrit, platelet count, AST, ALT, total bilirubin, alkaline phosphatase, blood urea nitrogen (BUN), creatinine, glucose, amylase, sodium, potassium, chloride, bicarbonate, qualitative urinalysis, microscopic urinalysis.

8.3.1.8 Evaluability Criteria

Three study populations of interest were identified by the sponsor using the following evaluability criteria:

- All Treated Patients: All patients who received at least one dose of study drug.
- Eligible Patients: All treated patients with a diagnosis of acute maxillary sinusitis at entry, defined as per inclusion criteria above.
- Clinically Evaluable Patients: All eligible patients who:
  - Received 80 – 120% of his/her study drug (or at least three days of therapy for treatment failures),
  - Received a final follow-up assessment (Test of Cure Visit within the Day +19 to Day +30 window; not applicable to treatment failures),
  - Did not receive any systemic antibacterials between the pre-treatment visit and the Test of Cure visit.

MO Comment: The evaluability criteria are acceptable for the clinically evaluable population. As described in detail in the following section, the sponsor used an expansion of the original "Final Follow-up Visit (Day +21 to +28)" as the test of cure visit.

8.3.1.9 Statistical Analyses

Pretreatment patient characteristics were summarized for the All Treated Patients, Eligible Patients, and Clinically Evaluable Patients. Prognostic factors, by treatment group, were also summarized by frequency, median, and minimum/maximum, where applicable.

Efficacy

Each patient was assigned a clinical response, based on the following criteria, at the Day +19 to Day +30 visit:

- CURE
  - ✓ All signs and symptoms of the acute infection were improved or resolved with the original therapy alone, without need for further antimicrobials. In addition, no new signs or symptoms of acute infection were present.

- FAILURE

  - ✓ Lack of improvement of signs and symptoms of the acute infection after at least three days of study drug therapy; or
  - ✓ Improvement or resolution of signs and symptoms of the acute infection at the end-of-treatment assessment (Day +1 to Day +3) followed by the recurrence of signs and symptoms at a subsequent follow-up assessment (either the Day +7 to Day +14 visit or the Test of Cure Visit in the Day +19 to Day +30 window).

- UNABLE TO DETERMINE
  - ✓ No post-treatment (within the Day +19 to Day +30 window) evaluation of signs and symptoms was done (i.e., no Test of Cure Visit); or
  - ✓ The patient received another systemic antibiotic with documented (i.e., in the package insert) activity against the principal pathogens associated with acute bacterial sinusitis, but for an infection other than sinusitis, prior to assessment at the Test of Cure Visit; or
  - ✓ The patient did not receive a minimum of three days of gatifloxacin therapy.

Primary Efficacy Analysis: Clinical cure rates in the clinically evaluable population for gatifloxacin and clarithromycin were compared, and a 95% confidence interval was constructed around the difference in cure rates. According to the original protocol, gatifloxacin would be considered no worse than clarithromycin if the confidence interval for the difference did not contain 15% (in favor of clarithromycin).

Secondary Efficacy Analysis: The analysis as outlined in the Primary Efficacy Analysis section above was also be applied to the Eligible Patients and All Treated Patients groups in the secondary efficacy analysis.

MO Comment: Clinical assessment of treatment response in the original protocol was based on both the end of treatment (Day +1 to Day +3) and final follow-up (Day +21 to Day +28) visits. In addition to the three possible clinical outcomes listed above, "early" and "late" relapse were also possible for patients who were "cured" at the end of treatment visit but who subsequently developed recurrent symptoms. This assessment scheme is similar to that recommended by the 1992 IDSA Guidelines for the Evaluation of Anti-Infective Drug Products.

A more recent draft evaluability criteria guidance document from the Division of Anti-Infective Drug Products recommends a single test of cure visit approximately 1-2 weeks following completion of therapy. Following consultation with the FDA, the sponsor revised the primary efficacy endpoint to be based solely on the clinical response at a single "Test of Cure" visit (Day +21 to Day +28). This change was implemented by sending out an administrative letter to all study sites dated 27 October 1997 (one month following initiation of the study).

The sponsor has since expanded the time window for the Test of Cure visit (Day +19 to Day +30 inclusive) to account for "potential schedule conflicts." The revised time window still allows sufficient time off study drug to assess treatment response and does not extend out far enough to raise concerns regarding re-infections. In an amendment to the NDA dated March 31, 1999, the sponsor states that these changes in the time window were implemented prior to database lock/unblinding of the data.

Safety

All patients receiving at least one dose of study drug were included in the safety analysis. Frequencies of adverse events were summarized by relationship to study drug, and displayed by primary term within the relevant body system as defined in a modified COSTART classification system. Adverse events considered to be drug related were also tabulated by severity.

Changes in lab values were assessed relative to pre-treatment values. Any worsening of values either during or post-therapy was graded on a 0 to 5 scale derived from the National Cancer Institute's Common Toxicity Criteria (CTC) or the Acquired Immune Deficiency Syndrome Clinical Trials Group (ACTG) classification of laboratory abnormalities.

8.3.1.10 Study Results

8.3.1.10.1 Database Validation

A 10% random sample of all patients enrolled in this trial was generated by the FDA statistical reviewer. The medical officer conducted an audit of all case report forms in this sample to assess the accuracy of transcription of data from the case report forms to the data sets used by the sponsor for the efficacy and safety analyses. No errors of transcription were identified by the audit.

MO Comment: The safety and efficacy data were faithfully transcribed from the case report forms to the sponsor's computerized database. The medical officer accepts the data sets submitted by the sponsor with the NDA as an accurate reflection of the study results.

8.3.1.10.2 Patient Population

A total of 425 patients were enrolled at 27 study sites in the United States and Canada as shown in the table below (modified from NDA, Volume 13, pg. 56) were randomized to gatifloxacin and 214 were randomized to clarithromycin. Approximately one-quarter of the total enrollment came from two investigators, Drs. McAdoo and Sullivan.

Patient Enrollment and Disposition By Investigator
Protocol AI420-008

Site Number/ Investigator	Number (%) of Total Patients			
	Enrolled	Treated	Eligible	Clinically Evaluable
013 M. McAdoo Milan Medical Center Milan, TN	60 (100)	60 (100)	59 (98)	47 (78)
029 J. G. Sullivan Parkway Medical Center Birmingham, AL	52 (100)	50 (96)	47 (90)	27 (52)
003 C. Fogarty Pharmaceutical Research Spartanburg, SC	27 (100)	27 (100)	25 (93)	22 (81)
005 R. Z. Paster Dean Medical Center Oregón, WI	24 (100)	24 (100)	22 (92)	22 (92)
008 A.Puopolo Milford Emerg. Assoc, Inc. Milford, MA	24 (100)	24 (100)	21 (88)	18 (75)
025 M. C. Audet Clinique Med.-Ste-Foy Quebec, Canada	23 (100)	23 (100)	23 (100)	21 (91)
001 F. P. Maggiacomo Silver Lake Medical Inc. Providence, RI	20 (100)	20 (100)	19 (95)	16 (80)
015 J. McCarty Hill Top Research Found. Fresno, CA	20 (100)	20 (100)	16 (80)	13 (65)
018 J. Champlin Clinical Research, Inc. Carmichael, CA	20 (100)	19 (95)	17 (85)	13 (65)
002 K. Wingert Sierra Medical Research Fresno, CA	14 (100)	14 (100)	11 (79)	8 (57)
012 R. R. Stoltz GFI Pharmaceutical, Inc. Evansville, IL	13 (100)	13 (100)	13 (100)	10 (77)
009 R. Slavin St. Louis University St. Louis, MI	12 (100)	12 (100)	8 (67)	8 (67)
020 R. Berkowitz Atlanta Allergy & Immunology Atlanta, GA	12 (100)	12 (100)	11 (92)	9 (75)
022 L. V. Larsen InterMt. Clinical Research Salt Lake City, UT	12 (100)	12 (100)	12 (100)	3 (25)

Site Number/ Investigator	Number (%) of Total Patients			
	Enrolled	Treated	Eligible	Clinically Evaluable
032 W. M. Gooch, III Med. Research Assoc. Utah Salt Lake City, UT	12 (100)	12 (100)	11 (92)	8 (67)
023 E. R. Brankston BBM Clinical Research Ontario, Canada	9 (100)	9 (100)	8 (89)	7 (78)
030 A.Kelly Hermitage Medicenter Alberta, Canada	9 (100)	9 (100)	8 (89)	7 (78)
011 B. M. Misken Palm Beach Research Center West Palm Beach, FL	8 (100)	8 (100)	5 (63)	5 (63)
019 J. Corren Allergy Research Foundation Los Angeles, CA	8 (100)	8 (100)	8 (100)	7 (88)
031 C. P. Mathew Woodmere Medical Center Harvey, LA	8 (100)	8 (100)	8 (100)	6 (75)
021 S. Peskind Carrolton, TX	7 (100)	7 (100)	7 (100)	6 (86)
006 M. Dennington S. Potomac Med. Research Aurora, CA	6 (100)	6 (100)	6 (100)	5 (83)
007 I.Tauber Tauber/Mahoney/ Oser, P.C. Silver Spring, MD	6 (100)	6 (100)	4 (67)	4 (67)
016 M. S. Doyle William Beaumont Hospital Ferndale, MI	6 (100)	6 (100)	6 (100)	4 (67)
027 D. M. McCarty Millwoods Medicentre Alberta, Canada	5 (100)	4 (80)	2 (40)	2 (40)
009 M. L. Brandon California Research Found. San Diego, CA	4 (100)	4 (100)	4 (100)	3 (75)
034 J. L. Williams Primary Care Center Trenton, TN	4 (100)	4 (100)	3 (75)	2 (50)
Total:	425	421	384	303

MO Comment: **The above investigators are acceptable. Enrolled patients were adequately distributed across study sites and geographical areas.**

8.3.1.10.3 Demographics

The following table was compiled from the NDA submission (Volume 13, pg. 61) and the medical officer's analysis of the data sets for the clinically evaluable patients:

Demography, All Treated Patients/Clinically Evaluable Patients
Protocol AI420-008

Characteristic	Gatifloxacin		Clarithromycin		Total	
	ITT* N = 210	Eval# N = 146	ITT N = 211	Eval N = 157	ITT N = 421	Eval N = 303
Gender [N (%)]						
Male	81(39)	61(42)	76(36)	54(34)	157(37)	115(38)
Female	129(61)	85(58)	135(64)	103(66)	264(63)	188(62)
Race [N (%)]						
White	187(89)	134(92)	192(91)	143(91)	379(90)	277(91)
Black	15(7)	8(5)	12(6)	9(6)	27(6)	17(6)
Hispanic	8(4)	4(3)	6(3)	4(3)	14(3)	8(3)
Other	0		1(<1)	1(<1)	1(<1)	1(<1)
Age (years)						
Mean	43	44	41	43	42	43
Median	42	44	41	43	42	43
Min. – Max.	18-79	18-77	18 – 80	18 – 80	18–80	18-80
Weight (kg)						
Mean	80	80	80	81	80	80
Median	77	78	76	77	77	77
Min. – Max.	43–150	47-146	43–181	43-181	43–181	43-181
Not Recorded	0	0	1	0	1	0

NOTE: Max. = Maximum; Min. = Minimum.

MO Comment: Patient randomization for the study resulted in very comparable demographic characteristics for the two treatment arms for the all-treated patients and clinically evaluable populations as shown above.

8.3.1.10.4 Reasons for Nonevaluability

From the NDA (Volume 13, pg. 61):

Distribution of Patients in Study Populations and Reasons for Exclusion
Protocol AI420-008

Study Population/Reason Excluded	Number (%) of Patients		
	Gatifloxacin	Clarithromycin	Total
All Treated	210 (100)	211 (100)	421 (100)
Eligible	185 (88)	199 (94)	384 (91)
Ineligible	25 (12)	12 (6)	37 (9)
Reason Ineligible:			
No Radiographic Documentation of Sinusitis	9 (4)	7 (3)	16 (4)
Missing Required Symptom(s) at Entry	9 (4)	1 (<1)	10 (2)
Chronic Sinusitis Rather Than Acute	5 (2)	4 (2)	9 (2)
Other	2 (1)	0	2 (<1)
Clinically Evaluable	146 (70)	157 (74)	303 (72)
Unevaluable	65 (31)	57 (27)	118 (28)
Reason Unevaluable:			
Ineligible	25 (12)	12 (6)	37 (9)
Post-treatment Follow-up Outside Window	16 (8)	11 (5)	27 (6)
Did Not Receive Minimum of 80% of Intended Study Drug Therapy (Excluding Failures)	9 (4)	16 (8)	25 (6)
No Test of Cure Visit	11 (5)	9 (4)	20 (5)
Other Systemic Antibiotic Received Prior to Post-treatment Follow-up	3 (1)	4 (2)	7 (2)
Other	0	2 (1)	2 (<1)

MO Comment: **The minor discrepancy in the number of clinically evaluable subjects between the two treatment arms is mainly due to more gatifloxacin patients failing to meet eligibility requirements with respect to clinical symptoms at entry. Individual review of these unevaluable gatifloxacin patients revealed that 8 of the 9 patients failed to meet the protocol requirement for purulent nasal secretions; the remaining patient failed to have the required sign/symptom of sinus tenderness/pain. Of note, all but one of these nine unevaluable gatifloxacin patients went on to clinical cure (i.e., their exclusion from the evaluable patient population did not favor the overall gatifloxacin clinical response rate). The other major reason for ineligibility was lack of radiological documentation of sinusitis, generally due to re-reading of the x-ray as normal by a radiologist or failure of radiographic findings to meet protocol specified criteria (e.g., lack of maxillary sinus involvement, less than 5 mm of mucosal thickening).**

A higher percentage of clarithromycin-treated patients were unevaluable due to not receiving at least 80% of intended study drug therapy, reflecting a higher incidence of adverse clinical events requiring discontinuation in that treatment arm (see *Safety Review*). No other bias with respect to treatment arm was apparent.

8.3.1.10.5 Prognostic Factors

The following table was compiled from the NDA submission (Volume 13, pg. 69) and the medical officer's analysis of the clinically evaluable patients using the NDA data sets:

Prognostic Factors, All-Treated Patients and Clinically Evaluable Patients Protocol AI420-008

Prognostic Factor	Number (%) of Patients					
	Gatifloxacin		Clarithromycin		Total	
	ITT* N = 210	Eval# N = 146	ITT N = 211	Eval N = 157	ITT N = 421	Eval N = 303
History of Sinusitis						
Yes	180(86)	124 (85)	178(84)	134(85)	358(85)	258(85)
No	30(14)	22(15)	33(16)	23(15)	63(15)	45(15)
Number of Sinusitis Episodes in Past 12 Months						
<3	149(71)	112(77)	159(75)	122(78)	308(73)	234(77)
≥3	60(29)	34(23)	52(25)	35(22)	112(27)	69(23)
Unknown	1		0		1	
Median	1	1	1	1	1	1
Minimum – Maximum	0 – 12	0 - 6	0 – 12	0 – 5	0 – 12	0 – 6
Prior Sinus Surgery						
Yes	20 (10)	17(12)	18(9)	15(10)	38(9)	32(11)
No	190(90)	129(88)	193(91)	142(92)	383(91)	271(89)
Allergic Rhinitis						
Yes	134(64)	94(64)	126(60)	98(62)	260(62)	192(63)
No	76(36)	52(36)	85(40)	59(38)	161(38)	111(37)
Bilateral Infection						
Yes	102(49)	76(52)	121(57)	88(56)	223(53)	164(54)
No	98(47)	70(48)	83(39)	69(44)	181(43)	139(46)
Normal	10 (5)	0	7(3)	0	17(4)	0

* ITT for this table refers to all treated patients
# Eval for this table refers to all clinically evaluable patients

MO Comment: The treatment arms were similar with respect to the above prognostic factors for both the all-treated and clinically evaluable patient populations. While allergic rhinitis and prior sinus pathology are recognized prognostic factors, the importance of bilaterality of infection is less clear.

8.3.1.10.5 Pre-treatment Signs/Symptoms

The following table was compiled from the NDA submission (Volume 13, pg. 65) and the medical officer's analysis of the clinically evaluable patients using the NDA data sets:

Primary Pre-treatment Signs and Symptoms of Acute Maxillary Sinusitis
Protocol AI420-008

Sign/Symptom[a]	Number (%) of Patients					
	Gatifloxacin		Clarithromycin		Total	
	ITT* N=210	Eval# N=146	ITT N=211	Eval N=157	ITT N=421	Eval N=303
Discharge, Nasal, Purulent	197(94)	142(97)	204(97)	152(97)	401(95)	249(96)
Congestion, Nasal	193(92)	135(92)	195(92)	149(95)	388(92)	284(94)
Pain, Sinus	188(90)	128(88)	198(94)	145(92)	386(92)	273(90)
Tenderness, Sinus	187(89)	131(90)	183(87)	139(89)	370(88)	270(89)
Pressure, Face	182(87)	130(89)	177(84)	130(83)	359(85)	260(86)
Postnasal Drip	172(82)	122(84)	173(82)	132(84)	345(82)	254(84)
Pain, Face	170(81)	121(83)	179(85)	132(84)	349(83)	253(83)
Headache	169(80)	115(79)	180(85)	133(85)	349(83)	248(82)
Coughing	162(77)	116(79)	167(79)	121(77)	329(78)	237(48)
Malaise	144(69)	97(66)	151(72)	115(73)	295(70)	212(70)
Sore Throat	125(60)	89(61)	128(61)	96(61)	253(60)	185(61)
Hyposmia	118(56)	82(56)	119(56)	90(57)	237(56)	172(57)
Pain, Dental	86(41)	63(43)	103(49)	76(48)	189(45)	139(46)
Chills	79(38)	58(40)	84(40)	66(42)	166(39)	124(41)
Halitosis	79(38)	60(41)	87(41)	65(41)	163(39)	125(41)
Swollen Sinus	76(36)	57(39)	82(39)	61(39)	158(38)	118(39)
Discharge, Nasal, Watery	73(35)	49(34)	73(35)	62(39)	146(35)	111(37)
Fever (>38°C/100.4°F)	6(3)	5(3)	4(2)	3(2)	10(2)	8(3)
Other	22(10)	15(10)	23(11)	17(11)	45(11)	32(11)

[a] Patients may be included in more than one category.

* ITT for this table refers to all treated patients
# Eval for this table refers to all clinically evaluable patients

MO Comment: The inclusion criteria for the study required purulent anterior or posterior nasal discharge or purulent discharge from the maxillary sinus ostium. However, the table above shows that only 97% of the evaluable study populations had purulent nasal discharge as a presenting sign/symptom. The medical officer reviewed the case report forms of the remaining 3% of patients to assess this discrepancy. While they did not have purulent nasal discharge checked off as presenting sign/symptom, they all did, in fact, have purulent nasal discharge noted on physical examination by the investigator.

Physical findings of acute sinusitis were similarly distributed across treatment arms for "all-treated" and clinically evaluable patient populations. Of note, no assessment of severity for symptoms (e.g., none, mild, moderate, severe) was performed at the pre-treatment visit. Subsequent assessments were only rated as "resolved," "improved," "same," or "worse."

8.3.10.1.6 Reasons for Discontinuation

From the NDA (Volume13, pg. 73):

Reasons for Discontinuation of Study Medication, All Treated Patients Protocol AI420-008

Reason Discontinued	Number (%) of Patients		
	Gatifloxacin N = 210	Clarithromycin N = 211	Total N = 421
Number Completed Therapy	181 (86)	186 (88)	367 (87)
Number Discontinued Prematurely	29 (14)	26 (12)	55 (13)
Adverse Clinical Event	10 (5)	18 (9)	28 (7)
Lost to Follow-up	5 (2)	3 (1)a	8 (2)a
Protocol Violation	4 (2)	1 (<1)	5 (1)
Intercurrent Illness	2 (<1)	2 (<1)	4 (<1)
Patient Request	3 (1)	1 (<1)	4 (<1)
Other Antibiotic Given	2 (<1)	0	2 (<1)
Inappropriate Diagnosis	1 (<1)	0	1 (<1)
Persistent Pre-treatment Nausea	1 (<1)	0	1 (<1)
Worsened Signs or Symptoms	1 (<1)	0	1 (<1)

[a] Includes one patient (-029-239) whose reason for discontinuation of study medication was inadvertently omitted from the database.

MO Comment: As noted above, a higher percentage of clarithromycin patients had adverse clinical events resulting in treatment discontinuation (see *Safety Review*). Otherwise, the reasons for discontinuance appear reasonable and not biased by treatment arm.

8.3.1.10.7 Baseline Radiological Findings

From the NDA (Volume 13, pg. 67):

**Pre-treatment Radiographic Data for Maxillary Sinuses,
All Treated Patients
Protocol AI420-008**

Finding	Number (%) of Patients		
	Gatifloxacin N = 210	Clarithromycin N = 211	Total N = 421
Normal	10 (5)	7 (3)	17 (4)
Abnormal	200 (95)	204 (97)	404 (96)
Mucosal Thickening Only	43 (20)	38 (18)	81 (19)
Opacification Only	42 (20)	40 (19)	82 (19)
Air/Fluid Level Only	12 (6)	10 (5)	22 (5)
Any Combination of Findings	103 (49)	116 (55)	219 (52)

MO Comment: The results above were reproduced by the medical officer's analysis of the data sets. Approximately 95% of imaging studies were sinus x-rays (plain films); the remaining studies were CT scans. Radiological findings on enrollment were comparable between the two treatment arms. Patients with "normal" x-rays were typically enrolled with a tentative radiological diagnosis of sinusitis by the investigator, and the films were later read as normal by the radiologist. These patients were catergorized as "ineligible" and were, therefore, clinically unevaluable.

8.3.1.10.8 Study Drug Exposure

From the NDA (Volume 13, pg. 71):

Study Medication Usage, All Treated Patients
Protocol AI420-008

Extent of Dosing	Number (%) of Patients		
	Gatifloxacin N = 210	Clarithromycin N = 211	Total N = 421
Number of doses			
<16	17 (8)	20 (9)	37 (9)
16	1 (<1)	- -	1 (<1)
17 – 21	3 (1)	4 (2)	7 (2)
22	1 (<1)	- -	1 (<1)
23 – 27	21 (10)	24 (11)	45 (11)
28	161 (79)	161 (77)	322 (78)
Not Recorded	6	2	8
Duration (days)			
Mean (SD)	13 (3.02)	13 (3.27)	13 (3.15)
Median	14	14	14
Minimum - Maximum	1 – 15	1 – 23	1- 23
<8	17 (8)	19 (9)	36 (9)
8-10	2 (1)	3 (1)	5 (1)
11	1 (<1)	1 (<1)	2 (<1)
12 – 13	4 (2)	2 (1)	6 (1)
14	170 (83)	170 (81)	340 (82)
>14	11 (5)	14 (7)	25 (6)
Not Recorded	5	2	7

NOTE: SD = standard deviation.

MO Comment: The study drug exposures, as assessed by patient diaries and pill counts, were comparable in the all-treated patients group.

8.3.1.10.9 Efficacy

The medical officer compiled the results in the following table from various tables within the NDA (Volume 13, pp. 84, 88, and Appendix 9, pg. 1):

Clinical Response, Per Sponsor
Protocol AI420-008

	Number (%) of Patients								
Clinical Response	Gatifloxacin			Clarithromycin			Total		
	ITT* N = 210	Elig+ N = 185	Eval# N = 146	ITT N = 211	Elig N = 199	Eval N = 157	ITT N = 421	Elig N = 384	Eval N = 303
Cured[a]	131(62)	119(64)	105(72)	132(63)	129(65)	119(76)	263(62)	248(65)	224(74)
Failure	46(22)	43(23)	41(28)	43(20)	39(20)	38(24)	89(21)	82(21)	79(26)
Unable to Determine	33(16)	23(12)	0(0)	36(17)	31(16)	0(0)	69(16)	54(14)	0(0)
[a] 95% Confidence interval for the difference in Cure rate:				ITT = (-10.0, 9.6). Elig = (-10.9, 9.4) Eval = (-15.2, 6.7)					

*ITT for this table refers to all treated patients
+Elig for this table refers to all clinically eligible patients
#Eval for this table refers to all clinically evaluable patients

MO Comment: As previously noted, the definition of "cure" at the revised TOC visit (Day +19 to Day +30) was broadened to include patients in whom "all signs and symptoms of the acute infection have improved or resolved with the original therapy alone, without need for further antimicrobials." This change was implemented by an administrative letter sent to all study sites and the FDA (dated 27 October 1997). The sponsor's summary of the efficacy data in the table above shows that the response rates for gatifloxacin and clarithromycin were 72% and 76%, respectively (95% C.I.= -15.2, 6.7). Since the efficacy rates fell below the expected 80-90% range as outlined in the protocol, the sponsor states that the equivalence delta should be expanded to 0.20. Using the larger equivalence delta, the sponsor concludes that the criteria for equivalence are met.

The medical officer reviewed the signs/symptoms profiles for all patients at the TOC visit. Rigorous application of the sponsor's revised definition of "cure" would require *at least* improvement of all signs/symptoms of the acute infection, including those less specific for sinusitis (e.g., nasal congestion, coughing, chills). However, a large number of eligible and evaluable patients in each treatment arm designated as "cure" by the sponsor were noted to have signs/symptoms of sinusitis which had either remained the same or had worsened since the baseline pretreatment visit. The medical officer acknowledges that many of the signs/symptoms identified during pretreatment evaluation may have been related to medical conditions other than the acute infection (especially concomitant inhalant allergies). However, nasal purulent discharge and sinus pain/tenderness are "cardinal" signs/symptoms of acute sinusitis as noted by the sponsor and were required inclusion criteria for the study. Thus, one would expect complete resolution of nasal purulent discharge and sinus pain/tenderness at the TOC visit (i.e., a minimum of 19 days following completion of a ten to fourteen day course of study drug). Indeed, review of the medical literature suggests that the

symptoms of acute maxillary sinusitis should resolve within 5 days to 3 weeks following initiation of effective therapy[1,2].

Thus, the medical and statistical reviewers reanalyzed the efficacy data, requiring resolution of at least purulent nasal discharge and local pain/tenderness signs/symptoms for a patient to be considered a "cure" (see table below). This analysis shows a response rate of 61% and 66% for gatifloxacin and clarithromycin, respectively, in the evaluable patient population (95% C.I. = -16.5, 6.6). Of note, two gatifloxacin patients were designated as "unknown" regarding these cardinal symptoms at the TOC visit. If these patients were assumed to be failures due to these unknown values, the response rate for evaluable patients would be 60.3% and 65.6% for gatifloxacin and clarithromycin, respectively (95% C.I. = -17.2, 5.9).

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Clinical Response, FDA Analysis #1

(Cure requires resolution of nasal purulence discharge and local pain/tenderness)

Protocol AI420-008

	Number (%) of Patients								
Clinical Response	Gatifloxacin			Clarithromycin			Total		
	ITT N = 210	Elig N = 185	Eval N = 146	ITT N = 211	Elig N = 199	Eval N = 157	ITT N = 421	Elig N = 384	Eval N = 303
Cured[a]	113(54)	102(55)	89(61)	112(53)	110(55)	103(66)	225(53)	212(55)	192(63)
Failure	64(30)	60(32)	57(39)	63(30)	58(29)	54(34)	127(30)	118(31)	111(37)
Unable to Determine	33(16)	23(12)	0(0)	36(17)	31(16)	0(0)	69(16)	54(14)	0(0)
[a] 95% Confidence interval for the difference in Cure rate:				ITT = (-9.0, 11.0) Elig = (-10.7, 9.9) Eval = (-16.5, 6.6)					

*ITT for this table refers to all treated patients
*Elig for this table refers to all clinically eligible patients
*Eval for this table refers to all clinically evaluable patients

A less rigorous analysis, which requires only improvement in these cardinal symptoms, is presented in the table below. In this second FDA analysis, cure rates for gatifloxacin and clarithromycin were 71% and 76%, respectively (95%C.I.= -16.6, 5.5) in evaluable patients.

Clinical Response, FDA Analysis #2

(Cure requires at least improvement of nasal purulence discharge and local pain/tenderness)

Protocol AI420-008

	Number (%) of Patients								
Clinical Response	Gatifloxacin			Clarithromycin			Total		
	ITT* N = 210	Elig* N = 185	Eval* N = 146	ITT N = 211	Elig N = 199	Eval N = 157	ITT N = 421	Elig N = 384	Eval N = 303
Cured[a]	129(61)	117(63)	103(71)	131(62)	128(64)	119(76)	260(62)	245(64)	222(73)
Failure	48(23)	45(24)	43(29)	44(21)	40(20)	38(24)	92(22)	85(22)	81(27)
Unable to Determine	33(16)	23(12)	0(0)	36(17)	31(16)	0(0)	69(16)	54(14)	0(0)
[a] 95% Confidence interval for the difference in Cure rate:				ITT = (-10.5, 9.1). Elig = (-11.6, 8.9) Eval = (-16.6, 5.5)					

*ITT for this table refers to all treated patients
*Elig for this table refers to all clinically eligible patients
*Eval for this table refers to all clinically evaluable patients

Clinical Response by Demographic Subsets

The medical officer performed the following exploratory analysis of the clinical response rate at the test of cure visit for various demographic subsets using the sponsor's data sets:

Clinical Response For Demographic Subsets
Protocol AI420-008

	Number (%) of Patients Cured					
Subset	Gatifloxacin		Clarithromycin		95% Confidence Interval of Difference in Cure Rates (G-C)	
	ITT*	Eval#	ITT*	Eval#	ITT*	Eval#
Female	77(60)	59(69)	87(64)	80(78)	(-0.18, 0.07)	(-0.23,0.06)
Male	52(64)	44(72)	44(58)	39(72)	(-0.10, 0.23)	(-0.20, 0.18)
18-65 years	116(61)	92(71)	121(61)	111(76)	(-0.10,0.11)	(-0.17,0.07)
≥ 65 years	13(62)	13(72)	10(77)	10(83)	(-0.53,0.20)	(-0.50,0.27)
White	115(61)	93(69)	123(64)	111(78)	(-0.13,0.08)	(-0.20,0.03)
Black	10(67)	6(75)	5(42)	5(56)	(-0.15,0.63)	(-0.29,0.71)
Latino/Hispanic	4(50)	4(100)	3(50)	3(75)	(-0.62,0.52)	(-0.52,0.83)

*ITT for this table refers to all treated patients
#Eval for this table refers to all clinically evaluable patients

MO Comment: This study was not designed or statistically powered to detect differences in efficacy among the subsets above. However, cure rates for clarithromycin generally tended to be higher than gatifloxacin in female patients, elderly patients and white patients.

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8.3.1.10. 10 Safety

Deaths

No patients died during the study.

Serious Adverse Events

Three serious adverse events occurred during the study, none of which were considered to be study-drug related by the investigator:

Study Drug	Patient No.	Study Day	Event
Gatifloxacin	025-422	+7	Moderately severe left cerebrovascular accident/right hemiparesis
Clarithromycin	020-441	+13	Mild, non-cardiac chest pain requiring hospitalization
Clarithromycin	029-257	4	Developed bilateral pneumonia while on study drug requiring discontinuation from the study

Adverse Events

Overall, 263 (62%) of enrolled patients experienced at least one adverse event. The most commonly reported events were rhinitis (15% gatifloxacin, 17% clarithromycin), nausea (13% gatifloxacin, 14% clarithromycin), and headache (11% in each arm). See NDA Volume 13, Appendix 12 for a complete listing of all reported adverse events.

In 170 (65%) of these patients, the adverse event was considered to be study drug-related by the investigator. The following table of drug-related adverse events by severity was obtained from the NDA submission (Volume 13, pg. 96):

Drug-Related Adverse Clinical Events, by Severity; All Treated Patients
Protocol A1420-008

	Number (%) of Patients									
	Gatifloxacin (N = 210)					Clarithromycin (N = 211)				
Adverse Clinical Event[a]	Mild	Moderate	Severe	Very Severe	Total	Mild	Moderate	Severe	Very Severe	Total
Any Drug-Related Adverse Clinical Event	39 (19)	25 (12)	11 (5)	0	75 (36)	44 (21)	36 (17)	14 (7)	1 (<1)	95 (45)
Nausea	17 (8)	5 (2)	5 (2)	0	27 (13)	16 (8)	5 (2)	3 (1)	0	24 (11)
Vaginitis[b]	6 (3)	4 (2)	1 (<1)	0	11 (5)	1 (<1)	1 (<1)	0	0	2 (<1)
Diarrhea	5 (2)	5 (2)	1 (<1)	0	11 (5)	11 (5)	7 (3)	0	0	18 (9)
Dyspepsia	3 (1)	5 (2)	0	0	8 (4)	7 (3)	2 (1)	0	0	9 (4)
Headache	3 (1)	4 (2)	1 (<1)	0	8 (4)	1 (<1)	5 (2)	2 (<1)	0	8 (4)
Pain, Abdomen	6 (3)	1 (<1)	0	0	7 (3)	4 (2)	7 (3)	1 (<1)	0	12 (6)
Taste Perversion	3 (1)	3 (1)	0	0	6 (3)	18 (9)	14 (7)	3 (1)	1 (<1)	36 (17)
Vomiting	1 (<1)	2 (<1)	1 (<1)	0	4 (2)	3 (1)	2 (<1)	3 (1)	0	8 (4)
Anorexia	3 (1)	0	0	0	3 (1)	0	1 (<1)	0	0	1 (<1)
Dry Mouth	1 (<1)	2 (1)	0	0	3 (1)	4 (2)	1 (<1)	1 (<1)	0	6 (3)
Nervousness	2 (<1)	1 (<1)	0	0	3 (1)	2 (<1)	0	0	0	2 (<1)
Tremor	3 (1)	0	0	0	3 (1)	0	2 (<1)	0	0	2 (<1)
Ulcer Mouth	1 (<1)	2 (<1)	0	0	3 (1)	0	0	0	0	0

[a] All drug-related adverse clinical events occurring in ≥1% or more of the patients in either treatment group.
[b] Percentages are based on the number of females in the respective treatment group.

MO Comment: The medical officer analyzed the adverse events database from the NDA submission and obtained similar results to those in the above table. Adverse events were generally only mild to moderate in severity. Gastrointestinal events (nausea, vomiting, diarrhea, abdominal pain, dyspepsia) were the most common overall and were the most common reason for treatment discontinuation.

The following adverse clinical events associated with other drugs in the fluoroquinolone class were not commonly seen with gatifloxacin therapy during this study:

Heptotoxicity:

No cases of acute liver failure or hepatotoxicity were reported.

Central Nervous System:

No cases of seizures, convulsions, or psychosis were reported during therapy. Dizziness was more common in the clarithromycin group (4%) than in the gatifloxacin group (1%). Only one elderly Hispanic female patient (AI420-008-018-121) required discontinuation of gatifloxacin due to dizziness. The relationship of her dizziness to the study drug was unclear because the patient had a past history of basilar artery insufficiency and vertigo. The low incidence of nervousness, paresthesias, and tremor were comparable between the two groups.

Tendonopathy:

No cases of rupture of the shoulder, hand or Achilles tendon were reported. One 55 year old white male patient developed a left plantar fasciitis of moderate intensity on Day 10 of gatifloxacin therapy. Another 39 year old white female developed a mild left elbow tendonitis on Day 11 of gatifloxacin therapy. The investigators judged both events to be unrelated to study drug therapy and neither case required treatment.

Rash:

Rashes were noted in 1% of gatifloxacin-treated patients and 2% of clarithromycin treated patients. Of the three drug-related rashes in the gatifloxacin group, two were rated as mild in intensity. The third was a moderately severe rash on the buttock and groin of a 25 year old white male (AI420-008-008-445) which required discontinuance of study drug. The rash worsened on alternative drug therapy (Augmentin), but the patient was lost to follow-up prior to resolution of the rash. Phototoxicity was not reported.

Anaphylaxis:

Serious and occasionally fatal hypersensitivity and/or anaphylactic reactions have been reported in patients receiving therapy with quinolones. Although not identified by the sponsor as such, two patients receiving gatifloxacin were discontinued from the trial due to signs and symptoms which could be consistent with an anaphylactic hypersensitivity reaction:

- Patient AI420-008-001-094, a 50 year old white female with a history of angina, hypertension, and kidney stones developed tingling and swelling of the tongue, dizziness, and mild nausea on Day 2 of gatifloxacin therapy, all of which resolved without treatment.

- **Patient AI420-008-010-118, a 44 year old black female with a history of asthma and recurrent sinusitis, developed severe throat tightness on Day 4 and again on Day 12 of therapy and decided to discontinue therapy the following day. Other adverse events reported by this patient during therapy included: intermittent heart palpitations (Days 5, 10), tinnitus (Days 6, 10), and intermittent tremors (Day 9).**

While not clearly allergy-mediated drug reactions, these two cases raise concern regarding the potential for anaphylactic reactions in patients receiving gatifloxacin therapy. Review of post-marketing adverse events should include a heightened awareness of this concern.

Cardiac Effects:

Routine electrocardiograms (ECG) were not obtained on patients enrolled in this study. Thus, no assessment of drug effects on QT interval is possible. However, cardiac-related symptoms were rare in the study. One patient in each arm of the study reported palpitations. The patient in the gatifloxacin arm (as previously discussed under the *Anaphylaxis* subsection) reported severe intermittent palpitations on Day 5 and moderately intense palpitations on Day 10 of study therapy. Both episodes were self-limiting and no formal workup (e.g. ECG) or treatment was pursued. The patient decided to discontinue study therapy on Day 11 due to her multiple adverse clinical events.

Clinical Laboratory Evaluation

None of the patients in this study were discontinued due to laboratory abnormalities. As shown in the table below (Volume 13, pg. 102), most of the abnormalities which occurred during study drug therapy were mild (Grade 1 by CTC/ACTG classification scale). Among gatifloxacin-treated patients with normal baseline lab values, decreased bicarbonate (12%) hyponatremia (11%), and increased bicarbonate (6%) were most commonly observed.

Abnormal liver function test values (transaminases, total bilirubin) were more commonly seen in the clarithromycin group. In the gatifloxacin group, all changes in transaminases were Grade 1, and total bilirubin elevations were Grade 2 (4 patients) or Grade 3 (2 patients).

Worsening of baseline lab abnormalities was uncommon in the gatifloxacin group. One patient each with abnormal hemoglobin, AST, and ALT worsened from a Grade 1 to a Grade 2 abnormality. Only one patient with a baseline Grade 2 abnormality of total bilirubin worsened to a Grade 3 abnormality. Worsening of baseline laboratory abnormalities was more common in the clarithromycin group (a total of 7 patients).

Abnormal Laboratory Test Values During or Post-Treatment in Patients with Normal Pre-treatment Values, All Treated Patients
Protocol A1420-008

Laboratory Test	Number (%) of Patients									
	Gatifloxacin (N = 210)					Clarithromycin (N = 211)				
	N[a]	Grade 1	Grade 2	Grade 3	Grade 4	N[a]	Grade 1	Grade 2	Grade 3	Grade 4
Hematology										
Hemoglobin	194	2 (1)	0	0	0	199	2 (1)	0	0	0
WBC	193	3 (2)	1 (<1)	0	0	202	6 (3)	0	0	0
Neutrophils	191	4 (2)	1 (<1)	0	0	199	3 (2)	0	0	0
Platelets	191	3 (2)	0	0	0	202	3 (1)	0	0	0
Liver Function										
AST/SGOT	190	3 (2)	0	0	0	201	8 (4)	0	0	0
ALT/SGPT	181	6 (3)	0	0	0	191	15 (8)	0	0	0
Alkaline Phosphatase	187	0	0	0	0	192	4 (2)	0	0	0
Total Bilirubin	194	0	4 (2)	2 (1)	0	195	0	9 (5)	2 (1)	0
Renal Function										
BUN	197	2 (1)	0	0	0	204	3 (1)	0	0	0
Creatinine	197	1 (<1)	0	0	0	203	1 (<1)	0	0	0
Pancreatic Function										
Amylase	194	5 (3)	0	0	0	200	3 (2)	0	0	0
Electrolytes										

Laboratory Test	Number (%) of Patients									
	Gatifloxacin (N = 210)					Clarithromycin (N = 211)				
	N[a]	Grade 1	Grade 2	Grade 3	Grade 4	N[a]	Grade 1	Grade 2	Grade 3	Grade 4
Hyponatremia	179	19 (11)	0	0	0	185	13 (7)	0	0	0
Hypernatremia	179	2 (1)	0	0	0	185	0	0	0	0
Hypokalemia	193	2 (1)	1 (<1)	0	0	200	4 (2)	0	0	0
Hyperkalemia	193	1 (<1)	0	0	0	200	0	0	0	0
Hypochloremia	195	1 (<1)	0	0	0	201	1 (<1)	0	0	0
Hyperchloremia	195	0	0	0	0	201	0	0	0	0
Decreased Bicarbonate	178	21 (12)	0	0	0	186	18 (10)	0	0	0
Increased Bicarbonate	178	9 (5)	1 (<1)	0	0	186	4 (2)	0	0	0

[a] For each test, number of patients with a normal pre-treatment value who had at least one during- or post-treatment value determined.

MO Comment: As noted in the NDA submission (Volume 25, pg. 223), "clinically relevant laboratory" abnormalities were defined as Grade 3 or 4 using the CTC/ACTG scale derived by the sponsor. The medical officer concurs with this classification scheme. Using this scheme, clinically relevant abnormalities were uncommon in both treatment arms and are accurately conveyed by the proposed labeling. The majority of laboratory abnormalities were mild (Grade 1), and effects on liver function tests were more common in the approved comparator arm. Of note, the NDA submission included serum glucose values on only a small subset of patients within this study. The medical officer requested this information from the sponsor in a memorandum dated 30 March 1999. The sponsor noted that many of the serum glucoses were obtained in the non-fasting state which complicates their interpretation. However, the sponsor submitted the complete serum glucose data across all indications as an amendment to the NDA. These data will be reviewed by Dr. Korvick as part of the integrated summary of safety.

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8.3.1.11 Medical Officer's Conclusions

The design and conduct of this randomized, double-blinded, comparative clinical trial were generally acceptable. Baseline signs, symptoms and radiographic findings of enrolled patients were consistent with the diagnosis of acute sinusitis. According to the sponsor, the clinical efficacy rates at the test of cure visit (Day +19 to Day +30 post-therapy) for gatifloxacin and clarithromycin in the evaluable patient population were 72% and 76%, respectively, with a 95% confidence interval (C.I.) of (-15.2,6.7) for the difference in efficacy rates. The sponsor's efficacy rates for the all-treated patients population were 62% and 63% for gatifloxacin and clarithromycin, respectively, 95% C.I. (-10, 9.6). The original protocol projected efficacy rates of 80-90% with an equivalence delta of 0.15. Due to the lower actual efficacy rates encountered in this study, the sponsor maintains that the equivalence delta should be 0.20. Using an equivalence delta of 0.20, the sponsor concludes that the criteria for equivalence are met.

The medical officer's review of the sponsor's efficacy determinations at the test of cure visit revealed that some patients with persistent or worsening of the cardinal signs/symptoms of acute maxillary sinusitis (i.e., maxillary sinus pain/tenderness and nasal purulent discharge) were designated as "cures." A more conservative FDA analysis, which required at least improvement in these cardinal signs/symptoms, showed efficacy rates in clinically evaluable patients of 61% and 66% for gatifloxacin and clarithromycin, respectively, 95% C.I. (-16.6, 5.5).

Review of the safety data in this study revealed that drug-related adverse events were more frequent in the clarithromycin comparator arm than in the gatifloxacin arm (45% and 36% of patients, respectively). The most common events in the gatifloxacin arm were related to the gastrointestinal tract (nausea, diarrhea, dyspepsia, abdominal pain) and were mild in severity. Two cases of possible Type I hypersensitivity reactions (tongue swelling, throat tightness) were noted in the gatifloxacin group, both of which reportedly resolved without treatment. However, post-marketing surveillance should include a heightened awareness of this potential adverse clinical event. Clinical laboratory abnormalities were uncommon and generally comparable to those seen in the active control arm, although liver function test abnormalities were more commonly noted in the clarithromycin arm.

The medical officer concludes that the efficacy data provided by this study only marginally, at best, demonstrates equivalence to the approved comparator agent, clarithromycin. As the only controlled, comparative study in the original NDA submission, it would probably not provide sufficient support for the approval of gatifloxacin for the indication of acute sinusitis. However, the sponsor has since submitted another supportive comparative clinical trial as an NDA amendment

(Amendment 15) which is reviewed in Section 8.3.3 below. The safety profile for gatifloxacin was acceptable and comparable to that of clarithromycin.

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8.3.2 Study No. AI420-007: "An Open-Label Multicenter Non-Comparative Phase II/III Study of Oral Gatifloxacin in the Treatment of Acute, Uncomplicated Bacterial Sinusitis in Patients Undergoing Sinus Aspirate"

8.3.2.9 Objectives:

The protocol-specified objectives of this study were to:

- Establish the clinical and bacteriologic efficacy of gatifloxacin at a dose of 400 mg QD in the treatment of acute, uncomplicated bacterial sinusitis where pathogenic organisms were verified by sinus aspirate; and
- Evaluate the safety profile of gatifloxacin at 400 mg QD in this patient population.

MO Comment: As suggested in the "Points to Consider" document from the Division of Anti-Infective Drug Products, this open-label study is designed to establish successful clinical and microbiological outcomes in patients with acute sinusitis caused by the major pathogens for this indication. Although not explicitly stated in the objectives, the duration of therapy studied was ten days.

8.3.2.2 Protocol Overview

This was an open-label, non-comparative Phase II/III study designed to assess the safety and efficacy of gatifloxacin, 400 mg PO QD X 10 days in the treatment of adults with acute, uncomplicated bacterial sinusitis for whom oral, outpatient therapy was indicated. This study focused on gatifloxacin's bacteriologic eradication rates for the major pathogens in acute bacterial sinusitis: *S. pneumoniae, H. influenzae,* and *M. catarrhalis.*

8.3.2.3 Inclusion Criteria

Inclusion criteria for this study were identical to those used in Study AI-420-008. See listing and MO Comments in the preceding protocol review.

8.3.2.4 Exclusion Criteria

Exclusion criteria were identical to Study AI-420-008 with the following exceptions:

- HIV positive status was not specifically listed as an exclusion criterion
- Previous treatment in other gatifloxacin trials was not listed as an exclusion criterion
- Concurrent terfenadine was not listed as an exclusion criterion

MO Comment: As in Study AI420-008, the inclusion/exclusion criteria were generally acceptable for enrollment of patients who likely had a diagnosis of acute bacterial sinusitis.

8.3.2.5 Study Procedures/Observations

As shown in the flow chart below (from NDA, Volume 14, pg. 31), the design and conduct of this study was very similar to that for Protocol AI40-008 with the exception of the microbiological diagnostic procedures and the lack of a comparator control arm:

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Flow Chart: Schedule of Patient Assessments
Protocol AI420-007

Procedure	Pre-treatment (within 48 hrs prior to dosing)	During Treatment (Day 3 to Day 5)	End of Treatment (Day +1 to Day +3)	Post-treatment[a] (Day + 7 to Day +14)	Final Follow-up (Day + 21 to Day +28)
Informed Consent	X	-	-	-	-
Inclusion/Exclusion	X	-	-	-	-
Sinus Radiograph	X	-	-	-	X
Medical History	X	-	-	-	-
Physical Exam	X	-	X	-	X
Nasal Exam	X	-	X	-	X
Vital Signs	X	X	X	-	X
Gram Stain (Sinus Aspirate)	X	X[b]	X[b]	-	X[b]
Sinus Aspirate Culture	X	X[b]	X[b]	-	X[b]
Subculture	X	X[b]	X[b]	-	X[b]
Clinical Signs and Symptoms	X	X	X	X[c]	X
Laboratory Tests	X	X	X	-	X[d]
Adverse Event Reporting	-	X	X	X	X
Assess Medication Use	-	X	X	-	-
Pregnancy Test	X	-	X	-	-

[a] Telephone contact.

[b] Not required if patient responds to treatment; should be obtained prior to initiation of alternate antibiotic therapy for all patients who fail to respond to treatment.

[c] If not clinically improved, the patient should be scheduled for an office visit for completion of the procedures outlined for the post-treatment visit (Section 5.8.5).

[d] If clinically indicated (i.e., all abnormal during/post-treatment laboratory test results should be repeated until they return to pre-treatment levels).

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Sinus Aspiration Procedure

The inferior meatus region was suctioned clear of secretions followed by application of Betadine™ or other topical antiseptic. Following topical anesthesia (cocaine or lidocaine) the medial antral wall was punctured with a large bore (e.g., 12 gauge) needle. If unable to aspirate fluid directly, the investigator instilled 1 cc of non-bacteriostatic saline, without preservative, into the antrum and then aspirated the irrigant. The air in the syringe was expelled and the syringe was capped and "delivered without delay" to the laboratory. Alternative routes for entry into the sinuses (e.g., canine fossa) were permitted.

MO Comment: The aspiration procedure is acceptable as described. Most clinicians will supplement the topical anesthetic with local injection of lidocaine to enhance pain control during the puncture. Of note, endoscopically-directed cultures of the middle meatus were not permitted in the study. As outlined in the DAIDP Evaluability Criteria Guidance document, the usefulness of endoscopic cultures has not been adequately documented in the literature, and *Staphylococcus aureus* contamination of specimens appears to be a significant problem with this technique.

Microbiologic Procedures

Gram stain, including leukocyte and epithelial cell counts were obtained under low power. Bacterial counts were obtained under high power. Quantitative cultures were obtained at the discretion of the individual investigator.

Additional testing for specific isolates was as follows:

Organism	Additional Testing
Haemophilus influenzae, parainfluenzae	β-lactamase, ampicillin sensitivity
Moraxella catarrhalis	β-lactamase
Streptococcus pneumoniae	penicillin sensitivity
Staphylococcus aureus	methicillin sensitivity

Subcultures of all causative organisms were to be sent to the sponsor using provided subculture kits.

MO Comments: Leukocyte count data from the sinus aspirates were not submitted in the NDA package. These data would primarily be useful in cases of suspected bacterial contaminants (e.g. *Staphylococcus aureus*) to support their role as a pathogen. However, the sponsor is pursuing a labeling claim for only the three major pathogens (*S. pneumoniae, H. influenzae,* and *M. catarrhalis*). These isolates, when recovered from an antral puncture, would be considered as pathogens regardless of leukocyte counts or bacterial colony counts.

8.3.2.6 Evaluability Criteria

The sponsor identified four study populations of interest using the following evaluability criteria:

All Treated Patients: All patients who received at least one dose of gatifloxacin.

Eligible Patients: All Treated Patients with a diagnosis of acute maxillary sinusitis at entry as defined in the inclusion criteria.

Clinically Evaluable Patients: All Eligible Patients who

- Received at least five days of treatment with gatifloxacin (at least three days for treatment failures),
- Received a final follow-up assessment (Test of Cure Visit within the Day +19 to Day +30 window; not applicable to treatment failures),
- Did not receive any systemic antibacterials between the time of the pre-treatment visit and the post-treatment assessment.

Microbiologically Evaluable Patients: All Clinically Evaluable Patients from whom a gatifloxacin non-resistant pathogen was isolated pre-treatment.

(Note: Only gatifloxacin non-resistant pre-treatment pathogens from these patients were considered for assessment of bacteriologic response.)

MO Comment: It is unclear why only 50% of the prescribed dose (5 days) was required for clinical evaluability rather than the standard 80-120%. Currently approved drugs generally require a minimum of 10 days of therapy for acute bacterial sinusitis, a closed space infection. Inclusion of patients receiving only 5 days of study therapy could increase the rates of failures or result in relapse of infection during or after the study period.

8.3.2.7 Endpoints

Clinical Response

As in Protocol AI420-008, clinical response was originally to be based on signs and symptoms of the infection under treatment at both the end-of-treatment and final follow-up visits. An Administrative letter issued on 27 October 1997 modified the timing of the efficacy assessment, and the clinical response was determined only at the final followup visit. Refer to review of Protocol AI420-008 above for definitions of clinical response (cured, failure, unable to determine).

Bacteriological Response

Bacteriologic response for pre-treatment pathogens was based either on culture results, or if there was no source to culture, the clinical assessment at the Test of Cure visit as described above. The following responses were assigned as follows:

ERADICATED:

The original pathogen was absent from the culture of the repeat sinus aspirate specimen.

PRESUMED ERADICATED:

The clinical response was Cured and no repeat sinus aspiration was performed.

PERSISTED:

The original pathogen was present in the culture of the repeat sinus aspirate specimen.

PRESUMED PERSISTED:

The clinical response was Failure and no repeat sinus aspiration was performed.

UNABLE TO DETERMINE:

The patient received another systemic antibiotic with documented (i.e., in the package insert) activity against the pre-treatment pathogen, for an infection other than sinusitis, prior to assessment at the Test of Cure Visit, or

The patient's pre-treatment pathogen was resistant to gatifloxacin, or

No post-treatment (within the Day +19 to Day +30 window) evaluation of signs and symptoms was done (i.e., no Test of Cure Visit), or

The patient did not receive a minimum of three days of gatifloxacin therapy.

MO Comment: The clinical and bacteriological endpoints are acceptable.

8.3.2.8 Statistical Analysis Plan

Sample Size

The sponsor targeted obtaining at least 20 isolates of each of the principal pathogens of acute bacterial sinusitis (*S. pneumoniae*, *H. influenzae* and *M. catarrhalis*) to "reliably determine eradication rates." For twenty patients with a given pre-treatment pathogen, it was asserted "with 95% confidence that the eradication rate for that pathogen was 71% or greater, as long as there were no more than three non-responders." Based on the frequency of isolation of the major pathogens in this disease, a total enrollment of 250 patients was estimated.

MO Comment: The DAIDP Points to Consider Document recommends isolation of at least 25 isolates each of *Streptococcus pneumoniae* and *Haemophilus influenzae*, and 15 isolates of *Moraxella catarrhalis* to demonstrate bacteriological efficacy against these major pathogens in acute sinusitis.

Efficacy

The clinically evaluable patients formed the primary data set for analysis of clinical efficacy, and the Microbiologically Evaluable Patients formed the primary data set for analysis of bacteriologic efficacy.

Safety

Safety data were analyzed in the same manner as in Protocol AI420-008.

8.3.2.9 Study Results

8.3.2.9.1 Database Validation

A 10% random sample of all patients enrolled in this trial was generated by the FDA statistical reviewer. The medical officer conducted an audit of all case report forms in this sample to assess the accuracy of transcription of data from the case report forms to the data sets used by the sponsor for the efficacy and safety analyses. No errors of transcription were identified by the audit.

MO Comment: The safety and efficacy data were faithfully transcribed from the case report forms to the sponsor's computerized database. The medical officer accepts the data sets submitted by the sponsor with the NDA as an accurate reflection of the study results.

8.3.2.9.2 Patient Population

A total of 445 patients were enrolled at 27 sites between 15 April 1997 and 5 April 1999. One hundred twenty-two patients (27%) were enrolled in countries other than the U.S.: 63 in Mexico (sites 029, 030, 033, and 035), 39 in Argentina (site 036), 15 in Australia (site 040), and 5 in South Africa (sites 021, 022, 023, and 026).The following table from the NDA (Amendment 20, Volume 1, pg. 61) summarizes enrollments and evaluability by study center:

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Patient Disposition
Protocol AI420-007

Study Center	Investigator	Number (%) of Total Patients				
		Enrolled	Treated	Eligible	Clinically Evaluable	Microbiol. Evaluable
-035	Dr. Jose Alberto Lopez Sisniega	40 (100)	40 (100)	40 (100)	34 (85)	19 (48)
-036	Guillermo Kaminszczik, MD	39 (100)	39 (100)	37 (95)	28 (72)	9 (23)
-037	David Hugh Frazer, Jr., MD	35 (100)	35 (100)	34 (97)	32 (91)	8 (23)
-004	Gregory M. Gottschlich, MD	25 (100)	25 (100)	24 (96)	18 (72)	3 (12)
-008	Phillip McElvaine, MD	24 (100)	22 (92)	18 (75)	14 (58)	4 (17)
-049	Walter N. Gaman, MD	24 (100)	24 (100)	24 (100)	20 (83)	7 (29)
-056	Roy W. Jones, MD	24 (100)	24 (100)	24 (100)	17 (71)	10 (42)
-011	Richard W. Nielsen, MD	23 (100)	23 (100)	23 (100)	22 (96)	7 (30)
-053	James E. Jarrett, MD	23 (100)	23 (100)	21 (91)	19 (83)	3 (13)
-045	Trevor I. Goldberg, MD	18 (100)	18 (100)	16 (89)	14 (78)	3 (17)
-014	Birgit Winther, MD	17 (100)	17 (100)	17 (100)	13 (76)	2 (12)
-043	Joseph D. Diaz, MD	17 (100)	17 (100)	16 (94)	14 (82)	3 (18)
-005	Samuel R. Hirsch, MD	16 (100)	16 (100)	15 (94)	14 (88)	5 (31)
-040	Jeff A. Karrasch, MD	15 (100)	15 (100)	13 (87)	9 (60)	6 (40)
-007	Michael S. Ellis, MD	11 (100)	11 (100)	11 (100)	10 (91)	5 (45)
-057	Neal S. Beckford, MD	11 (100)	11 (100)	10 (91)	6 (55)	1 (9)
-058	Robert A. Bonneau, MD	11 (100)	11 (100)	11 (100)	7 (64)	1 (9)
-033	Alfredo Mascareno, MD	9 (100)	9 (100)	8 (89)	2 (22)	2 (22)
-034	Jimmy Durden, MD	9 (100)	9 (100)	9 (100)	7 (78)	3 (33)
-029	Jorge Cruz Ponce, MD	7 (100)	7 (100)	7 (100)	3 (43)	3 (43)
-030	Javier Dibildox, MD	7 (100)	7 (100)	7 (100)	7 (100)	5 (71)
-042	C. Andrew DeAbate, MD	7 (100)	7 (100)	7 (100)	6 (86)	5 (71)
-012	M. Scott Touger, MD	6 (100)	6 (100)	6 (100)	2 (33)	1 (17)
-009	W. James Metzger, MD	5 (100)	5 (100)	5 (100)	5 (100)	1 (20)

Indication: Acute Sinusitis
Revision Date: 21-Oct-99

Study Center	Investigator	Number (%) of Total Patients				
		Enrolled	Treated	Eligible	Clinically Evaluable	Microbiol. Evaluable
-003	C. Wayne Gates, MD	4 (100)	4 (100)	4 (100)	2 (50)	1 (25)
-006	Robert J. Holloway, MD	4 (100)	4 (100)	3 (75)	3 (75)	0
-047	Presley M. Mock, MD	3 (100)	3 (100)	3 (100)	2 (67)	1 (33)
-010	Dennis N. Morrison, DO	2 (100)	2 (100)	2 (100)	2 (100)	0
-023	I. Jardine, MD	2 (100)	2 (100)	2 (100)	2 (100)	0
-061	Guy M. Handley, MD	2 (100)	2 (100)	2 (100)	1 (50)	1 (50)
-021	M. G. Gill, MD	1 (100)	1 (100)	1 (100)	1 (100)	0
-022	R. L. van der Nest, MD	1 (100)	1 (100)	1 (100)	1 (100)	0
-026	M. Goldin, MD	1 (100)	1 (100)	1 (100)	0	0
-044	Charles D. Hanshaw, DO	1 (100)	1 (100)	1 (100)	1 (100)	0
-054	Dennis J. Mikolich, MD	1 (100)	1 (100)	1 (100)	1 (100)	0
Total		445	443	424	339	119

NOTE: Microbiol. = Microbiologically.

MO Comment: The investigators listed above are acceptable. The two sites with greatest enrollment were non-U.S. sites, and twelve of the 27 sites enrolled 5 or fewer patients over the two-year period. These findings likely reflect the difficulty in enrolling patients in antral puncture studies in the U.S.

8.3.2.9.3 Demographics

The following table was obtained from the NDA (Amendment 20, Volume 1, pg. 66):

Demography, All Treated Patients
Protocol AI420-007

Characteristic	N = 443
Gender [N (%)]:	
Female	273 (62)
Male	170 (38)
Race [N (%)]:	
White	298 (67)
Hispanic	92 (21)
Black	47 (11)
Asian	2 (< 1)
Other	4 (< 1)
Age (years):	
Mean	40
Median	38
Minimum – Maximum	18 – 88
Weight (kg):	
Mean	77
Median	74
Minimum – Maximum	48 – 149
Not Recorded	2

MO Comment: The gender, age and weight demographic characteristics of this population are similar to the population in the AI420-008 study. However, a higher percentage of Hispanic patients were enrolled in this study (from the Mexican and Argentian sites).

8.3.2.9.4 Pretreatment Signs/Symptoms and Prognostic Factors/Pre-Treatment Radiological Findings

MO Comment: Please refer to the NDA (Amendment 20, Volume 1, pp. 70,72, 82) for a detailed listing of baseline signs/symptoms, prognostic factors, and pretreatment radiological findings. All were very similar to the characteristics of the two treatment arms in the AI420-008 study reviewed above. Nearly all enrolled patients had purulent nasal discharge, nasal congestion and sinus pain, consistent with the diagnosis of sinusitis. Most of patients (73%) had a prior history of sinusitis and 56% of patients had a history of allergic rhinitis. With respect to x-ray findings, over half of the patients enrolled had a combination of the following abnormalities consistent with sinusitis: opacification, mucosal thickening, air/fluid level.

8.3.2.9.5 Reasons for Nonevaluability

The following table was obtained from the NDA review (Amendment 20, Volume 1, pg. 64):

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ON ORIGINAL

Distribution of Patients in Study Populations and Reasons for Exclusion Protocol AI420-007

Study Population/Reason Excluded	Number (%) of Patients N = 445
All Treated	**443 (100)**
Eligible	**424 (96)**
Ineligible	**19 (4)**
Reason Ineligible:	
Missing Required Symptom(s) at Entry	7 (2)
Other	7 (2)
No Radiological Documentation	5 (1)
Clinically Evaluable	**339 (77)**
Unevaluable	**104 (23)**
Reason Unevaluable:	
Test of Cure Visit Outside the Day +19 to Day +30 Window	56 (13)
Ineligible	19 (4)
No Test of Cure Visit	11 (2)
Other Systemic Antibiotic Received Prior to Post-treatment Follow-up	10 (2)
Improper/Inadequate Dosage	8 (2)
Microbiologically Evaluable	**119 (27)**
Unevaluable	**324 (73)**
Reason Microbiologically Unevaluable:	
No Pre-treatment Pathogen	284 (64)
Clinically Unevaluable	39 (9)
Pre-treatment Pathogen Resistant to Gatifloxacin	1 (< 1)

MO Comment: The medical officer reviewed the datasets and found that all patients designated as clinically evaluable had 1) documentation of both the nasal purulent discharge and the sinus pain/tenderness entry criteria, 2) received at least 8 days of treatment unless early treatment failure (although the inclusion criteria only require 5 days), and 3) received a test of cure visit within the Day +19 to +30 time window.